

## **IN THE CLAIMS**

Please amend the claims in the following manner:

1. (original) A method of performing RNA interference, said method comprising exposing a double stranded polynucleotide to a target nucleic acid, wherein said double stranded polynucleotide is comprised of a sense strand and an antisense strand, and wherein said sense strand is substantially nonfunctional.
2. (original) The method according to claim 1, wherein said sense strand comprises at least one 2'-O-alkyl modification.
3. (original) The method according to claim 2, wherein said sense strand comprises at least one cytosine- or uracil-containing nucleotide base, and said at least one cytosine- or uracil-containing nucleotide base has a 2'-O-methyl modification.
4. (original) The method according to claim 2, wherein said 2'-O-alkyl modification is a 2'-O-methyl modification.
5. (original) The method according to claim 4, wherein said at least one 2'-O-methyl modification is on the first, second, eighteenth and/or nineteenth nucleotide base.
- 7 6. (currently amended) The method according to claim 1, wherein the sense strand further comprises a 5' conjugate.
- 8 7. (currently amended) The method according to claim 7 6, wherein the conjugate is cholesterol.
- 9 8. (currently amended) The method according to claim 1, wherein the sense strand comprises a cap on its 3' end.

~~10~~ 9. (currently amended) The method according to claim ~~9~~ 8, wherein the cap is an inverted deoxythymidine or two consecutive ~~2'-O-methyl~~ 2'-O-methyl modified nucleotides.

~~11~~ 10. (currently amended) The method according to claim 1, wherein said antisense strand comprises at least one modified nucleotide.

~~12~~ 11. (currently amended) The method according to claim ~~11~~ 10, wherein the at least one modified nucleotide is a 2'-halogen-modified nucleotide.

~~13~~ 12. (currently amended) The method according to claim ~~12~~ 11, wherein the 2'-halogen modified nucleotide is a 2'-fluorine-modified nucleotide.

~~14~~ 13. (currently amended) The method according to claim 1, wherein the sense strand comprises one or more cytosine- and/or uracil-containing nucleotide bases, and each of said one or more cytosine- and/or uracil-containing nucleotide bases is 2'-fluorine modified.

~~15~~ 14. (currently amended) A method of performing RNA interference, said method comprising exposing a double stranded polynucleotide to a target nucleic acid, wherein said double stranded polynucleotide comprises

- (a) a conjugate;
- (b) a sense strand comprising at least one 2'-O-alkyl modification, wherein said sense strand is substantially nonfunctional; and,
- (c) an antisense strand comprising at least one 2'-fluorine modification, wherein said sense and antisense strands form a duplex of 18-30 base pairs.

~~16~~ 15. (currently amended) The method according to claim ~~15~~ 14, wherein said at least one 2'-O-alkyl modification is on the first, second, eighteenth and/or nineteenth nucleotide base.

~~17~~ 16. (currently amended) The method according to claim ~~15~~ 14, wherein the conjugate is a 5' conjugate.

~~18~~ 17. (currently amended) The method according to claim ~~15~~ 14, wherein the conjugate is cholesterol.

~~19~~ 18. (currently amended) The method according to claim 1, wherein the sense strand further comprises a cap on its 3' end.

~~20~~ 19. (currently amended) The method according to claim ~~19~~ 18, wherein the cap is an inverted deoxythymidine or two consecutive ~~2'-O-methyl~~ 2'-O-methyl modified nucleotides.

Please add the following new claims:

20. (new) A method of performing RNA interference, said method comprising exposing a double stranded polynucleotide to a target nucleic acid, wherein said double stranded polynucleotide is comprised of a sense strand and an antisense strand, and wherein at least one of said sense strand and said antisense strand comprises at least one orthoester modified nucleotide.

21. (new) The method according to claim 20, wherein said at least one orthoester modified nucleotide is located on said sense strand.

22. (new) The method according to claim 21, wherein the antisense strand comprises at least one nucleotide selected from the group consisting of a 2' halogen modified

nucleotide, a 2' amine modified nucleotide, a 2'-O-alkyl modified nucleotide and a 2' alkyl modified nucleotide.

23. (new) The method according to claim 22, wherein the antisense strand comprises at least one 2' halogen modified nucleotide and said halogen is fluorine.

24. (new) The method according to claim 21, wherein the double stranded polynucleotide further comprises a conjugate.

25. (new) The method according to claim 24, wherein said conjugate is selected from the group consisting of amino acids, peptides, polypeptides, proteins, sugars, carbohydrates, lipids, polymers, nucleotides, polynucleotides, and combinations thereof.

26. (new) The method according to claim 24, wherein the conjugate is cholesterol.

27. (new) The method according to claim 24, wherein conjugate is polyethylene glycol.

28. (new) The method according to claim 20, wherein the double stranded polynucleotide comprises 18-30 nucleotide base pairs.

29. (new) The method according to claim 28, wherein the double stranded polynucleotide comprises 19 nucleotide base pairs.

30. (new) The method according to claim 20, wherein the double stranded polynucleotide has an overhang of at least one nucleotide unit on at least one of said sense strand and said antisense strand.

31. (new) The method according to claim 20, wherein at least one strand of the double stranded polynucleotide comprises at least one modified internucleotide linkage.

32. (new) The method according to claim 31, wherein the modified internucleotide linkage is selected from the group consisting of a phosphorothioate linkage and a phosphorodithioate linkage.

33. (new) The method according to claim 20, wherein at least one strand of the double stranded polynucleotide is a polyribonucleotide.

34. (new) A method of performing RNA interference, said method comprising exposing a double stranded polynucleotide to a target nucleic acid, wherein said double stranded polynucleotide is comprised of:

- (i) a sense strand,
- (ii) an antisense strand, and
- (iii) a conjugate,

wherein at least one of said sense strand and said antisense strand comprises a 2' modified nucleotide.

35. (new) A double stranded polynucleotide comprising:

- (a) a sense strand, wherein said sense strand comprises a polynucleotide that is comprised of at least one orthoester modified nucleotide; and
- (b) an antisense strand, wherein said antisense strand comprises a polynucleotide that is comprised of at least one 2' modified nucleotide.

36. (new) The double stranded polynucleotide of claim 35, wherein the antisense strand comprises at least one nucleotide selected from the group consisting of a 2' halogen modified nucleotide, a 2' amine modified nucleotide, a 2'-O-alkyl modified nucleotide and a 2' alkyl modified nucleotide.

37. (new) The double stranded polynucleotide of claim 36, wherein the 2' modified nucleotide is a 2' halogen modified nucleotide and said halogen is fluorine.
38. (new) The double stranded polynucleotide of claim 35, further comprising a conjugate.
39. (new) The double stranded polynucleotide of claim 38, wherein said conjugate is selected from the group consisting of amino acids, peptides, polypeptides, proteins, sugars, carbohydrates, lipids, polymers, nucleotides, polynucleotides, and combinations thereof.
40. (new) The double stranded polynucleotide of claim 38, wherein said conjugate is cholesterol.
41. (new) The double stranded polynucleotide of claim 38, wherein said conjugate is polyethylene glycol.
42. (new) The double stranded polynucleotide of claim 35, wherein said double stranded polynucleotide is comprised of 18-30 nucleotide base pairs.
43. (new) The double stranded polynucleotide of claim 42, wherein said double stranded polynucleotide is comprised of 19 nucleotide base pairs.
44. (new) The double stranded polynucleotide of claim 35, further comprising an overhang of at least one nucleotide unit on at least one of said sense strand and said antisense strand.

45. (new) The double stranded polynucleotide of claim 35, wherein at least one of said sense strand and said antisense strand comprises at least one modified internucleotide linkage.

46. (new) The double stranded polynucleotide of claim 45, wherein the modified internucleotide linkage is selected from the group consisting of a phosphorothioate linkage and a phosphorodithioate linkage.

47. (new) The double stranded polynucleotide of claim 35, wherein at least one of said sense strand and said antisense strand is a polyribonucleotide.

48. (new) A double stranded polynucleotide comprising:

- (a) a sense strand, wherein said sense strand comprises a polynucleotide that is comprised of at least one orthoester modified nucleotide;
- (b) an antisense strand, wherein said antisense strand comprises a polynucleotide that is comprised of at least one 2' modified nucleotide; and
- (c) a conjugate.

49. (new) The double stranded polynucleotide of claim 48, wherein the conjugate is located on the sense strand.

50. (new) The double stranded polynucleotide of claim 48, wherein the conjugate is located on the antisense strand.

51. (new) The double stranded polynucleotide of claim 48, wherein the antisense strand comprises at least one nucleotide selected from the group consisting of a 2' halogen modified nucleotide, a 2' amine modified nucleotide, a 2'-O-alkyl modified nucleotide and a 2' alkyl modified nucleotide.

52. (new) The double stranded polynucleotide of claim 51, wherein the sense strand is comprised of a 2' halogen modified nucleotide and said halogen is fluorine.

53. (new) The double stranded polynucleotide of claim 48, wherein the conjugate is selected from the group consisting of amino acids, peptides, polypeptides, proteins, sugars, carbohydrates, lipids, polymers, nucleotides, polynucleotides, and combinations thereof.

54. (new) The double stranded polynucleotide of claim 48, wherein the conjugate is cholesterol.

55. (new) The double stranded polynucleotide of claim 48, wherein the conjugate is polyethylene glycol.

56. (new) The double stranded polynucleotide of claim 48, wherein said polynucleotide is comprised of 18-30 nucleotide base pairs.

57. (new) The double stranded polynucleotide of claim 56, wherein said polynucleotide is comprised of 19 nucleotide base pairs.

58. (new) The double stranded polynucleotide of claim 48, further comprising an overhang of at least one nucleotide unit on at least one of said sense strand and said antisense strand.

59. (new) The double stranded polynucleotide of claim 48, wherein at least one of said sense strand and said antisense strand comprises at least one modified internucleotide linkage.



60. (new) The double stranded polynucleotide of claim 59, wherein the modified internucleotide linkage is selected from the group consisting of a phosphorothioate linkage and a phosphorodithioate linkage.

61. (new) The double stranded polynucleotide of claim 48, wherein at least one of said sense strand and said antisense strand is a polyribonucleotide.

62. (new) A double stranded polynucleotide comprising:

- (a) a sense strand comprised of at least one orthoester modified nucleotide;
- (b) an antisense strand; and
- (c) a conjugate.

63. (new) The double stranded polynucleotide of claim 62, wherein said conjugate is located on the sense strand.

64. (new) The double stranded polynucleotide of claim 62, wherein said is located on the antisense strand.

65. (new) The double stranded polynucleotide of claim 62 wherein the antisense strand comprises at least one nucleotide selected from the group consisting of a 2' halogen modified nucleotide, a 2' amine modified nucleotide, a 2'-O-alkyl modified nucleotide and a 2' alkyl modified nucleotide.

66. (new) The double stranded polynucleotide of claim 65, wherein the antisense strand is comprised of a 2' halogen modified nucleotide and said halogen is fluorine.

67. (new) The double stranded polynucleotide of claim 62, wherein the conjugate is selected from the group consisting of amino acids, peptides, polypeptides, proteins,

sugars, carbohydrates, lipids, polymers, nucleotides, polynucleotides, and combinations thereof.

68. (new) The double stranded polynucleotide of claim 62, wherein the conjugate is cholesterol.

69. (new) The double stranded polynucleotide of claim 62, wherein the conjugate is polyethylene glycol.

70. (new) The double stranded polynucleotide of claim 62, wherein the polynucleotide is comprised of 18-30 nucleotide base pairs.

71. (new) The double stranded polynucleotide of claim 70, wherein the polynucleotide is comprised of 19 nucleotide base pairs.

72. (new) The double stranded polynucleotide of claim 62, further comprising an overhang of at least one nucleotide unit on at least one of said sense strand and said antisense strand.

73. (new) The double stranded polynucleotide of claim 62, wherein at least one of said sense strand and said antisense strand comprises at least one modified internucleotide linkage.

74. (new) The double stranded polynucleotide of claim 62, wherein at least one of said sense strand and said antisense strand is a polyribonucleotide.

75. (new) A double stranded polynucleotide comprising:

- (a) a sense strand;
- (b) an antisense strand; and

(c) a conjugate;

wherein the sense strand and/or the antisense strand comprises at least one 2' modified nucleotide.

76. (new) The double stranded polynucleotide of claim 75, wherein the 2' modified nucleotide is selected from the group consisting of a 2' halogen modified nucleotide, a 2' amine modified nucleotide, a 2'-O-alkyl modified nucleotide and a 2' alkyl modified nucleotide.

77. (new) The double stranded polynucleotide of claim 76, wherein the 2' modified nucleotide is a 2' halogen modified nucleotide and said halogen is fluorine.

78. (new) The double stranded polynucleotide of claim 75, wherein the conjugate is selected from the group consisting of amino acids, peptides, polypeptides, proteins, sugars, carbohydrates, lipids, polymers, nucleotides, polynucleotides, and combinations thereof.

79. (new) The double stranded polynucleotide of claim 75, wherein the conjugate is cholesterol.

80. (new) The double stranded polynucleotide of claim 75, wherein the conjugate is polyethylene glycol.

81. (new) The double stranded polynucleotide of claim 75, wherein said polynucleotide is comprised of 18-30 nucleotide base pairs.

82. (new) The double stranded polynucleotide of claim 75, wherein said polynucleotide is comprised of 19 nucleotide base pairs.

83. (new) The double stranded polynucleotide of claim 75, further comprising an overhang of at least one nucleotide unit on at least one of said sense strand and said antisense strand.

84. (new) The double stranded polynucleotide of claim 75, wherein at least one of said sense strand and said antisense strand comprises at least one modified internucleotide linkage.

85. (new) The double stranded polynucleotide of claim 84, wherein the modified internucleotide linkage is selected from the group consisting of a phosphorothioate linkage and a phosphorodithioate linkage.

86. (new) The double stranded polynucleotide of claim 75, wherein at least one of said sense strand and said antisense strand is a polyribonucleotide.

87. (new) A double stranded polyribonucleotide comprising:

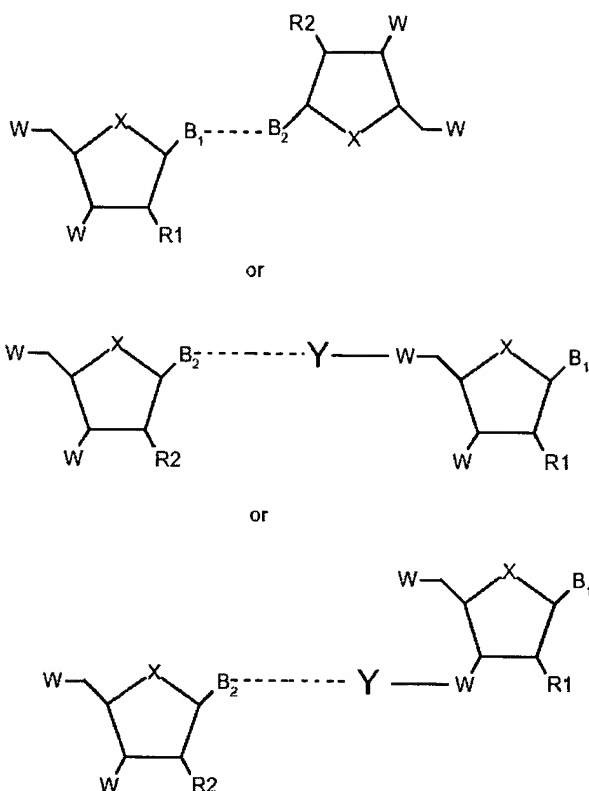
(a) a sense strand, wherein said sense strand is comprised of at least one 2' orthoester modified nucleotide;

(b) an antisense strand, wherein said antisense strand is comprised of at least one 2' modified nucleotide selected from the group consisting of a 2' halogen modified nucleotide, a 2' amine modified nucleotide, a 2'-O-alkyl modified nucleotide, and a 2' alkyl modified nucleotide; and

(c) a conjugate selected from the group consisting of amino acids, peptides, polypeptides, proteins, sugars, carbohydrates, lipids, polymers, nucleotides, polynucleotides, and combinations thereof;

wherein said polyribonucleotide comprises between 18 and 30 nucleotide base pairs.

88. (new) A composition comprising:



wherein:

each of  $B_1$  and  $B_2$  is a nitrogenous base, heterocycle or carbocycle;

X is selected from the group consisting of O, S, C, and N;

W is selected from the group consisting of an OH, a phosphate, a phosphate ester, a phosphodiester, a phosphotriester, a modified internucleotide link, a conjugate, a nucleotide, and a polynucleotide;

$R_1$  is an orthoester;

$R_2$  is selected from the group consisting of a 2'-O-alkyl group, an alkyl group, and amine, and a halogen; and

Y is a nucleotide or polynucleotide.